Emerging Optical Methods for Endoscopic Barrett's Surveillance

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Abstract

Barrett's oesophagus is an acquired metaplastic condition that predisposes patients to the development of oesophageal adenocarcinoma, prompting the use of surveillance regimes to detect early malignancy for endoscopic therapy with curative intent. The currently accepted surveillance regime uses white light endoscopy together with random biopsies, but suffers poor sensitivity and discards information from numerous light-tissue interactions that could be exploited to probe structural, functional and molecular changes in the tissue. Advanced optical methods are now emerging that are exquisitely sensitive to these changes and hold significant potential to improve surveillance of Barrett's oesophagus if they can be applied endoscopically. The next decade will see some of these exciting new methods applied to Barrett's surveillance in new device architectures for the first time, potentially leading to a long-awaited improvement of the standard of care.

Introduction

Barrett's oesophagus is an acquired metaplastic condition that predisposes patients to the development of oesophageal adenocarcinoma (OAC)[1]. The progression to cancer occurs through an intermediate stage known as dysplasia, which can be of low-grade (LGD) or high-grade (HGD). The cancer risk in non-dysplastic Barrett's oesophagus is estimated to range from 0.1 to 0.5%/year[2], but it increases to up to 9% in the presence of LGD[3] and it is 4 times higher in patients harbouring HGD, compared to patients with LGD[4]. As the 5-year survival rate for oesophageal cancer is just 15%, but improves to 80% in patients with early-stage cancer[5,6], major advisory bodies recommend that patients with Barrett's oesophagus undergo routine endoscopic surveillance for signs of dysplasia or early carcinoma[7–11]. Given the steep rise in cancer risk in patients with dysplasia, when LGD, HGD or in-situ carcinoma are detected there is indication to treat the early neoplastic lesion endoscopically with curative intent. Indeed, data from some retrospective studies indicate that endoscopic surveillance correlates with improved survival[12,13], although evidence from a case-controlled study[14] did not confirm this and data from randomised controlled trials is lacking.

The current standard of care (SOC) for endoscopic surveillance uses high-definition white light endoscopy (HD-WLE) to identify suspicious lesions, then histopathological analysis of biopsied tissue for diagnosis **(Supplementary Figure 1)**. To mitigate the risk of missing subtle, flat lesions, the protocol includes taking random biopsies at four-quadrant positions, in addition to targeted biopsies of visible lesions[7]. The resulting sensitivity is 40%-64% with specificity of 98-100%[15], but the procedure is costly, time-consuming and prone to sampling error[11]. The potential to improve clinical outcomes by detecting dysplasia with advanced optical methods has driven a great deal of research in this area.

White light endoscopy discards information from a wide range of contrast mechanisms **(Figure 1)** that can be exploited by more advanced optical methods to determine the disease state of tissue. In this review, we use the term 'optical method' to refer to the combination of an underlying contrast mechanism with an endoscope-compatible device, which results in a signal that can be used to guide the endoscopist. With demand for endoscopy predicted to rise substantially over the next decade[16], the unmet clinical need for optical methods with improved diagnostic yield and lower device cost / complexity is particularly acute.

Advanced optical methods are categorised as 'red-flag', 'optical biopsy' or hybrid. Red-flag methods provide wide-field images and if they provide sufficient contrast for dysplasia, can replace the random four-quadrant biopsies through improved targeted biopsy. A recent study estimated that using a targeted biopsy protocol alone could reduce per-patient biopsy costs from ~£1000 to ~£30[17]. Conversely, optical biopsy methods measure a small area of tissue with the goal of providing *in vivo*, real-time diagnosis, which could ultimately replace physical biopsy and enable

surveillance and intervention to occur within the same procedure. Hybrid methods, as the name suggests, combine red flag and optical biopsy capabilities to identify and diagnose disease *in vivo*.

The field of advanced endoscopy has been described in several recent reviews[9,15,18,19]. Here, we summarise the current status of the field with a focus on newly emerging optical methods, considering in particular the impact of device architecture on clinical translation. We conclude with a perspective on the potential for improvements in the endoscopic surveillance of Barrett's oesophagus.

Emerging endoscopic device architectures

At present, clinical endoscopic surveillance of Barrett's oesophagus is performed using a forward-facing trans-oral endoscope architecture, around which standard endoscopic tools, such as biopsy forceps and treatment devices, have been designed. Forward-facing endoscopes require articulation by the endoscopist to ensure complete surveillance of the tissue. A key consideration in the development and clinical translation of new optical methods is whether this remains the appropriate device architecture. An obvious and naïve approach to advanced endoscopy is simply to integrate the new optical imaging method into an existing forward-facing endoscope, to exploit familiarity of endoscopists with the presented images and retain access to the usual endoscopic tools. In recent years, research groups and commercial companies have taken a more 'out-of-the-box' approach, developing a host of alternative device architectures that overcome some or all of the limitations of forward-facing endoscopy, namely: low magnification; high procedure cost; the need for specialist operators; and restricted angular field of view **(Table 1 and Figure 2).**

Accessory channel endoscopes, or 'babyscopes', enable small-diameter probes to be inserted into standard forward-facing endoscopes through the channel that is normally used to introduce tools. They provide enhanced image data, often placed in direct contact with oesophageal tissue for optical biopsy methods. Unlike physical biopsy, increasing the number of these optical biopsies does not add significantly to procedure cost, however, the endoscopist must manually control the position the babyscope, so the results will still be subject to sampling error. In addition to this, the physiological movements of the oesophagus due to peristalsis and anatomic vicinity to the heart, make stabilization of the microscopic image challenging. In other cases, rather than direct contact, the imaging device employs a balloon that is inflated to ensure a fixed distance between the tissue and the central axis of the imaging hardware[20,21].

The high procedure cost of forward-facing endoscopy arises from the need for patient sedation in a specialist facility with a skilled endoscopist. Unsedated trans-nasal endoscopy (UTNE) provides standard endoscopy capabilities (imaging, articulation, insufflation, suction, biopsy) in a slim device that can be used without sedation, as the trans-nasal intubation does not involve contact with the root of the tongue and therefore does not trigger the

gagging reflex. UTNE has been successfully used for imaging BO and oesophageal dysplasia[22–24]. Multiple UTNE systems are commercially available, including two disposable devices which make reprocessing feasible outside of a hospital environment[25]. Recent studies using UTNE in screening for BO have found it to be comparable to standard endoscopy in clinical effectiveness, participation and safety[26] and considerably cheaper, especially if implemented in a mobile unit instead of a hospital[27]. Nonetheless, UTNE image quality is currently insufficient for dysplasia detection in surveillance setting.

While UTNE still requires a skilled endoscopist, wireless capsule endoscopes are single-use, pill-shaped devices that can be administered by a non-specialist operator. Originally developed for small bowel imaging[28], wireless capsules have since been developed for the oesophagus[29]. When surveyed, most patients prefer capsule endoscopy to regular endoscopy[30], which may improve adherence to surveillance protocols. Capsule endoscopy has become the gold standard for the small bowel, but studies in the oesophagus have yielded mixed results[31]. Wireless capsules have several significant limitations in the oesophagus[32]: the need for a reclined ingestion protocol to increase the imaging period during swallowing from seconds to minutes[31]; difficulty in identifying the capsule location for a given image; and the inability to take biopsies during the procedure.

Tethered capsule endoscopes retain the benefits of wireless capsules while addressing several of their limitations in the oesophagus by using a cord to control the capsule's position[33]. The tethered capsule is swallowed by the patient in an upright position, then imaging is performed while it is pulled back up from the stomach. The tethered architecture eliminates the risk of capsule retention and opens up the possibility of capsule re-use, which could lower per-procedure costs[34]. A tethered capsule architecture for Barrett's surveillance is currently in clinical trials[35].

Finally, increased inspection time has been associated with an increased HGD/OAC detection rate in HD-WLE Barrett's surveillance[36], however, it is unclear whether this relates to longer time spent by the endoscopists in characterizing lesions detected during the examination. Inspection time is affected by the need of careful articulation of the endoscope to bring the entire luminal surface within the 160-180° forward-facing field of view. Wide angle endoscopes[37] with a 330° field of view have been successfully demonstrated in the colon. One study found that this decreased the colonic adenoma miss rate from 41% to 7%[38] compared to standard forward facing devices although this was not confirmed in a recent randomised study[39]. Wide angle or stereoscopic devices[40], which allow 3D reconstruction, have yet to be implemented in the upper gastrointestinal tract but may improve surveillance.

Optical endoscopic methods used in clinical practice for BO surveillance

Several advanced optical methods, such as acetic acid chromoendoscopy, narrow band imaging and confocal laser endomicroscopy, have made their way into clinical use in some centres. Still, endoscopic practice varies significantly across countries and within the same country, and use of these advanced optical methods is often

restricted to tertiary referral centres delivering endoscopic treatment to a high volume of dysplastic patients. These methods have been extensively reviewed elsewhere[19,41], so we will only briefly summarise them here. For reference, **Table 2 and Supplementary Figure 2** show the current evidence, recommendation status, as well as key advantages and disadvantages of these methods. A recent meta-analysis by the American Society for Gastrointestinal Endoscopy (ASGE) suggest that to be recommended for targeting biopsy, a new technology should achieve at least 90% sensitivity, 80% specificity and 98% negative predictive value[18].

Chromoendoscopy enhances contrast through topically applied dyes. Acetic acid eliminates the superficial mucosal layer and then causes acetylation of cellular proteins, resulting in whitening that highlights surface patterns. In case of neoplastic Barrett's, this is rapidly followed by focal erythema caused by vascular congestion in stromal capillaries, which is revealed as focal redness as loss of acetowhitening occurs[17]. These reactions are used to guide targeted biopsies and increase the yield of dysplasia, meeting the ASGE performance thresholds[18,42]. Methylene blue chromoendoscopy has also been extensively investigated, but there are concerns regarding possible carcinogenic effects of the dye[43]. Meta-analyses have found it to be inferior to WLE[44] and acetic acid chromoendoscopy[18]. It is therefore likely that acetic acid will become the standard conventional chromoendoscopic method for BO surveillance.

Virtual (also known as electronic or optical) chromoendoscopy improves contrast by modifying the endoscope hardware or software. This avoids the challenges of working with dyes, such as increased procedure time for dye administration and potential for adverse effects caused by the dye. Hardware modifications reported to date usually involve adapting the light source to focus on blue and green wavelength bands, where the haemoglobins are strongly absorbing, providing contrast based on changes in the tissue vasculature[41]. Narrow band imaging (NBI) is the most widely established and also meets the ASGE thresholds[18]. NBI highlights the capillary network of the superficial mucosa and the operator classifies the disease state of the tissue based on altered vascular and mucosal patterns associated with dysplasia[45]. Blue laser imaging (BLI) is a similar technology that has also been tested in patients (*in vivo*, comparative study, n=39 patients)[46] and is under evaluation in Barrett's oesophagus[47]. Software-based virtual chromoendoscopy methods[48,49] use proprietary image processing algorithms to improve the contrast of mucosal and surface vessel patterns in the GI tract[50]. While there is not currently sufficient data for advisory bodies to make recommendations[18], clinical studies have shown that software-based approaches compare well to acetic acid chromoendoscopy (*in vivo*, prospective randomized pilot study, n=57)[51]. These early findings will need to be confirmed with large randomised controlled trials. Virtual chromoendoscopy has significant advantages in being label-free and easily applied in any WLE device architecture, including UTNEs[25] and capsules[52,53], so now has widespread availability.

While chromoendoscopy relies on light reflected from tissue, fluorescence imaging uses emission of a longer wavelength (or 'redder' colour) of light after illumination of the tissue to provide added contrast for dysplasia in endoscopic surveillance. Several structural and metabolic molecules intrinsic to tissue, such as collagen and NADH,

are fluorescent. Dysplastic tissue exhibits lower 'autofluorescence' than surrounding healthy tissue[54]. Autofluorescence imaging (AFI) has high sensitivity for dysplasia, but low specificity because inflammation also reduces tissue autofluorescence[55]. AFI is implemented by adding filters to the light source and detector on a standard endoscope, so has been combined with HD-WLE as well as virtual chromoendoscopy in endoscopic trimodal imaging (ETMI) in an effort to increase specificity. Trials to date have yielded mixed results [56,57]; it remains unclear whether AFI truly adds to the already improved performance of NBI.

In addition to the intrinsic fluorescence, intravenous fluorescein (a fluorescent dye) can be used to highlight microvasculature and tissue structures to detect dysplasia. This is commonly examined using confocal laser endomicroscopy (CLE), which produces depth-sectioned, high magnification and resolution images, which can be used to spot changes in cell morphology associated with dysplasia, yielding high sensitivity and specificity[18]. An endoscope-based CLE system (eCLE) was recommended by the ASGE[18], but requires a dedicated endoscope that is no longer on the market. A 'babyscope' probe-based CLE (pCLE) with lower resolution and limited depth sectioning, which can be inserted through the working channel of a standard forward facing endoscope is available. Clinical trial results to date indicate that pCLE can be used to identify neoplasia but is not yet sufficient to replace random biopsy[58]. Neither fluorescence approach is available in UTE format as yet; the feasibility of incorporating fluorescence imaging into capsule endoscopes is being explored[59].

Emerging optical methods for endoscopic BO surveillance: what is on the horizon?

While existing advanced endoscopy methods have shown potential for improving the identification of dysplasia during BO surveillance, a number of exciting recent advances have been made in optical imaging that could address outstanding limitations in sensitivity and specificity, ultimately reducing the high miss rate[15,60] **(Table 3 and Supplementary Figure 3)**. Given the aforementioned challenges with the use of dyes and the other excellent recent reviews of optical molecular imaging[61], we will concentrate here on label-free methods.

Interrogating disordered tissue structure

HD-WLE interrogates disordered tissue structure by presenting images of macroscopic abnormalities on the epithelial surface. Several recent advances have been made that allow endoscopists to probe cross-sectional information, up to several millimetres deep. Optical coherence tomography (OCT) can be thought of as 'optical ultrasound', with contrast derived from changes in refractive index rather than impedance mismatch. OCT uses scanning low-coherence interferometry to construct 3D reflectance images that reveal changes tissue microstructure arising due to variations in light scattering[62], giving excellent contrast for dysplasia[63]. Endoscopic applications of OCT

were made feasible by the shift from time-domain OCT to optical frequency domain imaging (OFDI), which significantly increased data acquisition rates. 3D images of the entire oesophagus can be acquired using an inflatable balloon babyscope device architecture, compatible with forward-facing endoscopes[20], or a rotating probe housed in a tethered capsule endoscope[33]. Both helical, luminal imaging approaches can be referred to as volumetric laser endomicroscopy (VLE). VLE has been successfully correlated with histology in BO patients[64] (*ex vivo*, feasibility study, n=14 matched resection specimens) and detects oesophageal neoplasia *in vivo*[63] (*in vivo*, patient series, n=6 patients). One challenge with VLE is enabling guidance of tissue biopsy, which is not compatible with the existing device architectures; a combination of VLE and laser cautery has been shown to safely mark regions of interest for later biopsy under HD-WLE guidance[65] (*in vivo*, pilot study, n=22 patients). A second challenge remains with image interpretation; an experienced OCT endoscopist is currently needed, limiting widespread deployment. Automated image analysis is being investigated to alleviate this burden and bring the method closer to the clinic[66,67].

In addition to providing contrast for OCT, variation in light absorption and scattering from tissue can be recorded as a function of wavelength or angle. Diffuse reflectance spectroscopy (DRS), also called elastic scattering spectroscopy (ESS), illuminates the tissue with a standard white light source, but instead of collecting an image of the oesophagus using a camera, changes in the colour of the light arising from absorption and scattering events in the superficial layers of the tissue are measured with a spectrometer, a device that disperses white light into its component colours. Contact (ESS)[68] and fixed-distance (DRS)[69] babyscope probes can differentiate between healthy and dysplastic tissue in the oesophagus, though are typically restricted to point-based measurements rather than endoscopic imaging.

Taking the concept a step further, light scattering spectroscopy (LSS) singles out reflected light that has only scattered once in tissue. The benefit of this approach is that LSS measurements can be directly linked to tissue morphology via physical Mie scattering theory, enabling quantitative measurements of the size and density of cell nuclei, which is associated with disease state[70]. An early LSS study achieved 90% sensitivity and specificity for oesophageal dysplasia[71] (*in vivo*, single centre pilot study, n=13 patients, n=76 sample positions) with a babyscope contact probe, but unwanted variations in probe-tissue separation led to challenges for interpretation. Hardware developments overcame this limitations to enable 8 cm segments of oesophagus to be mapped with 92% sensitivity and 96% specificity[72] (*in vivo*, single centre pilot study, n=9 patients, n=95 biopsies), showing potential for this to become a useful red-flag tool for guiding targeted biopsies in Barrett's surveillance. Angle-resolved low coherence interferometry (a/LCI) also looks at singly-scattered light but probes the angular scattering distribution of just a single colour of light. a/LCI has been shown to identify dysplasia (including LGD) with 100% sensitivity and 84% specificity *in vivo*[73] (*in vivo*, 2 centre pilot study, n=46 patients, n=172 sample positions) and a negative predictive value of 100%.

Although DRS, LSS and a/LCI were originally point measurement methods, the ability to provide 2D maps that co-register with HD-WLE or other images of tissue anatomy has now been demonstrated[69,74], although not yet tested

in vivo. There are also phase and polarisation-sensitive endoscopic methods on the horizon that derive contrast from scattering and present wide-field images[75,76]. While VLE is the most advanced method for interrogating microstructure in terms of clinical translation, if their performance remains high in randomised controlled trials, DRS, LSS and a/LCI have potential to become valuable tools to guide targeted biopsy.

Interrogating abnormal tissue function and metabolism

Virtual chromoendoscopy has been successful in improving targeted biopsy based on changes in tissue vasculature, but only interrogates superficial epithelial changes. OCT has shown exciting possibilities for cross-sectional imaging of tissue function, using measurements of blood flow to highlight the vasculature[77,78], although these have yet to be clinically validated. Another method that provides cross-sectional vascular information is photoacoustic endoscopy (PAE), which uses optical excitation of tissue to generate ultrasound[79]. The benefit of this approach is that highly optically absorbing molecules in tissue, such as haemoglobins, can be resolved at far greater penetration depth than is available from exclusively optical imaging. PAE could therefore directly provide high resolution cross-sectional virtual chromoendoscopy at centimetre depths, allowing visualisation of vascular patterns associated with dysplasia. PAE devices using a similar helical scanning implementation to OCT[80–82] have been applied in rabbit oesophagi[83], but further development is needed to increase radial resolution and acquisition speed, as well as to address challenges with image interpretation (similar to those of OCT). Recent successful studies using photoacoustic imaging in breast cancer diagnosis and other areas[84] suggests that application of PAE in Barrett's surveillance may yet yield valuable information, potentially in combination with OCT and other advanced methods[81].

Using a contrast mechanism already applied in the clinic, time-resolved assessment of tissue autofluorescence may overcome the present challenge of poor specificity in the interpretation of AFI. Changes in autofluorescence intensity, as measured by standard AFI endoscopes, can be confounded by surface irregularities and non-uniform illumination. Fortunately, measuring the lifetime of the fluorescence signal, rather than its absolute intensity, avoids these confounding factors[85]. Fluorescence lifetime microscopy (FLIM) is able to map changes in local tissue microenvironment and has shown promise in detection of cancers in *ex vivo* and *in vivo* studies[85]. For many years, the clinical translation of FLIM was limited by the size, cost and complexity of the instrumentation and the need for long integration times due to weak signals. A 2003 study of point-based fluorescence lifetime measurements found sensitivity and specificity for HGD of less than 60% using time resolved fluorescence[86] (*in vivo*, single centre pilot study, n=37 patients, n=108 fluorescence decay profiles). More recently, however, compact diode-pumped laser-based excitation sources and time-gated methods have addressed instrumentation limitations[87] meaning wide-field FLIM endoscopes with near-video rate acquisition (~2Hz)[88–90] are now available. While these have been used *in vivo*[88,91] they have yet to be applied to Barrett's surveillance and may yield improved performance in this context.

Complementing wide-field FLIM approaches, multi-photon microscopy (MPM) provides an autofluorescence-based alternative to pCLE. MPM is a scanning, optical sectioning, imaging approach in which fluorescence is spatially delineated using non-linear optical excitation. *Ex vivo* MPM of fresh punch biopsies can successfully distinguish squamous mucosa, gastric columnar mucosa and intestinal metaplasia[92] (*ex vivo*, n=25 patients, n=35 biopsies) suggesting that MPM could be used to identify dysplasia. MPM endoscopes are being developed and can incorporate additional features from microscopy such as super-resolution imaging[93]. Although MPM is at a very early stage of development, it holds potential to perform high magnification, depth-sectioned, label-free endomicroscopy as part of Barrett's surveillance.

Interrogating bulk molecular composition

Changes in bulk molecular composition can be determined using the spectral 'fingerprint' measured through Endoscopic Raman Spectroscopy (ERS), which is typically classified based on machine-learning methods that use a training set of spectra where the disease classification is known from histopathology analysis[94]. ERS is sensitive to the abundance of molecular bonds, primarily lipid, protein and nucleic acid content in tissue. ERS probes are typically introduced through a babyscope into a standard forward-facing endoscope and positioned directly on a suspicious region of tissue to provide a point-based measurement.

The low intensity of Raman signals has been a hurdle for ERS, historically resulting in very slow data acquisition. Nonetheless, Bergholt et al. recently demonstrated an ERS babyscope system, including a classification algorithm based on a Raman library of >12000 spectra, that could differentiate between columnar lined epithelium, non-dysplastic BO or HGD, in real time (0.2 sec), passing this information to the endoscopist using auditory feedback[95] (*in vivo*, pilot study, n=77 patients, sensitivity 87.0%, specificity 84.7%). Trans-nasal image-guided Raman spectroscopy has also been demonstrated[96]. Alternatively, Coherent Anti-stokes Raman Spectroscopy (CARS), which uses multiple photons to probe specific regions of the spectral fingerprint, has been suggested as a way to overcome the low Raman intensity and several prototype endoscopes have been developed, despite challenges associated with non-linear effects in fibres and the design of miniature optics[97,98]. Precision remains a challenge for ERS and ECARS, due to pressure-based signal variation, but prospective randomized multicentre trials are underway[95] and further devices are under development[99]. Raman spectroscopy is thus a promising method that could provide point measurements for optical biopsy and be scanned to assess larger areas of tissue if biopsy guidance were desired.

Multimodal methods

The recent advances highlighted above suggest that the intrinsic optical interactions with tissue have the potential to improve the diagnostic yield of Barrett's surveillance. Naturally, combining several of these into a single device architecture could have added benefits, giving access to structural, functional and molecular information simultaneously. For example, a recent pilot study with an intraoperative fibre probe combining DRS, ERS and fluorescence spectroscopy achieved 100% sensitivity and 93% specificity for several cancers[100].

Achieving a successful combination, however, requires careful optical design and often complex instrumentation. One promising route to overcoming this challenge may lie in the use of hyperspectral imaging (HSI), where the light illuminating the tissue and being imaged is dispersed into its component colours, or rapidly modulated. NBI is a simple example of this, where restricting illumination to two wavelengths highlights the vasculature in tissue due to strong haemoglobin absorption. HSI goes further, recording 10s or 100s of colours at every pixel in an endoscopic image, which can then be processed using machine-learning methods to resolve reflectance (e.g. NBI, BLI, DRS), fluorescence (AFI) or Raman (ERS) information into separate images. HSI has shown potential for aiding cancer diagnosis in a range of organ sites, including the oesophagus[101], although has yet to be demonstrated through *in vivo* trials in Barrett's surveillance. HSI hardware is often bulky and slow; optimisation of the HSI hardware, for example using compact spectrally resolved detector arrays[102], may assist in the future with real-time clinical application.

Introducing cross-sectional methods into such endoscopes adds a further challenge, particularly if helical scanning implementations are needed, as these typically require further endoscopist training to develop specialist expertise for interpretation. If true optical biopsy is to be achieved, cross-sectional information will be vital. The addition of scattering measurements that exploit other dimensions of light than colour, such as phase and polarisation[75,76] may help to achieve accurate depth-sectioning and hence improved identification of early dysplasia in the oesophagus.

Translational outlook for new optical methods

Novel optical imaging methods that probe structural, functional and molecular information in tissue hold significant potential to improve BO surveillance endoscopy. Clinical translation of these emerging optical methods, however, faces many challenges. The most appropriate device architecture for implementation of the optical method must first be identified. Next, the resulting endoscopic instrument must undergo technical and biological validation in phantoms, preclinical models and clinical trials to ensure performance and safety standards are met[103]. Several challenges can be encountered at this stage. For technical validation, the lack of calibration standards and accepted

internal exposure limits for optical diagnostic methods makes it difficult to assess the risks of potential thermal damage or photoallergic reactions for a new device[104]. Testing in *ex vivo* tissue does not provide an appropriate reference in this regard, since blood flow will dissipate heat. Furthermore, for biological validation, the optical properties of tissue can change markedly when examined *ex vivo*, which may limit the utility of subsequent *in vivo* findings[92,105]. Given the limited number of studies detailing the nature of changes in light-tissue interactions during the development of dysplasia, particular benefit for biological validation may be derived from further *ex vivo* and *in vivo* analysis of oesophageal tissue in different disease states.

Clinical trials at expert research centres with enriched populations or complex protocols may also bias findings, which can lead to disappointing results once deployment is more widespread[56,57]. For example, ASGE recommendations for use of acetic acid chromoendoscopy, NBI and eCLE for targeted biopsy assume the endoscopist has specialist training in image acquisition and interpretation for these methods. The use of histopathological diagnosis as the gold standard for evaluation of a new optical endoscopic device can also be confounding, since it itself is prone to sampling and interpretation errors[11,106]. Ideally, biopsies would be taken under guidance of a new optical method and subjected to consensus histopathology to minimise such errors. The alternative is to establish longitudinal studies that relate early-stage imaging parameters to late-stage clinical outcomes, which is extremely costly. Once devices and specialists are available across multiple sites, metrics to interpret the images must be developed and perfected, often by consensus of an expert group. This complex development process requires strong multidisciplinary collaboration, including expertise from medicine, engineering, physics, biomedical sciences, computer science and mathematics. Clear and open communication between those developing new endoscopic devices and those who will ultimately operate them is paramount.

The emerging optical methods reviewed here aim to either increase the contrast of wide-field ‘red flag’ endoscopic surveillance, for improved targeting of physical biopsies, or to provide an ‘optical biopsy’ that could yield diagnostic information directly during the endoscopic procedure. Enhancing the existing red-flag forward-facing endoscopy could be achieved through the addition of light scattering spectroscopy[72], but further clinical studies are needed to establish potential for improved BO surveillance. Hyperspectral endoscopy has the potential to enable a truly multi-modal red-flag and is the subject of ongoing work across a number of centres.

The majority of optical methods reviewed provide an optical biopsy. Several spectroscopic methods (DRS, LSS, a/LCI, ERS, ECARS) are compatible with forward-facing endoscopy using a babyscope and have the potential to be automated to give a fast real-time binary feedback to the endoscopist[73,95]. As their application becomes more widespread, the acquisition of more data will enable refinement of the automated classification algorithms, further improving sensitivity and specificity. Imaging methods applied for optical biopsy, such as CLE and MPM, also hold promise, particularly if they are able to achieve adequate depth sectioning to yield high quality images for

interpretation by histopathologists. Given the restricted field-of-view of such methods, they remain reliant on a high contrast red-flag endoscopy to achieve their diagnostic potential.

Hybrid approaches that combine red-flag and optical biopsy information, as well as structural and functional information, have also been demonstrated. Photoacoustic endoscopy is at an early stage, while volumetric laser endomicroscopy (VLE) is the most mature of the emerging methods described in this review, with a commercial system already available[20]. Furthermore, it has been demonstrated in both babyscope balloon and tethered capsule device architectures. If contact between the capsule device and the lumen can be maintained, VLE is able to capture high-resolution volumetric images of the entire oesophagus, an interesting niche. Although interpretation is currently performed offline, the development of automated diagnosis algorithms[66], accelerated by recent advances in machine learning coupled with increasingly inexpensive computing power, offers the possibility of a real-time computer-aided diagnosis. Such information could be combined with immediate laser cautery marking of suspicious lesions[65]. Though at present a standard forward-facing endoscope would still be required for physical biopsy and therapeutic intervention, the comprehensiveness, simplicity, and apparent achievability of VLE is exciting.

In summary, an ideal BO endoscopic surveillance method would perform comprehensive investigation of the oesophagus with high sensitivity and specificity for dysplasia. It should allow for use of endoscopic tools for marking and biopsy if necessary. It should also be possible to implement with minimal additional training of endoscopist operators and image interpreters. To achieve widespread deployment in healthcare systems, no significant change to procedure times or costs should be made; ideally these would be reduced. If possible, availability of endoscopy to BO patients should be increased, for example by enabling deployment by non-specialist operators in primary care centres, and physical discomfort with the procedure should be decreased, to improve compliance with surveillance programmes.

Though several advanced endoscopy methods have been recommended for routine use in Barrett's oesophagus, histological assessment of HD-WLE targeted and random biopsies is still the standard-of-care. Many emerging methods combine a contrast mechanism and device architecture to achieve some of the aforementioned requirements, but fall short of providing the ideal solution. Continuing advances in hardware and software are allowing endoscopic application of optical methods developed for other indications. The next decade will see some of these exciting new methods applied to Barrett's surveillance in new device architectures for the first time, potentially leading to a long-awaited improvement of the standard of care.

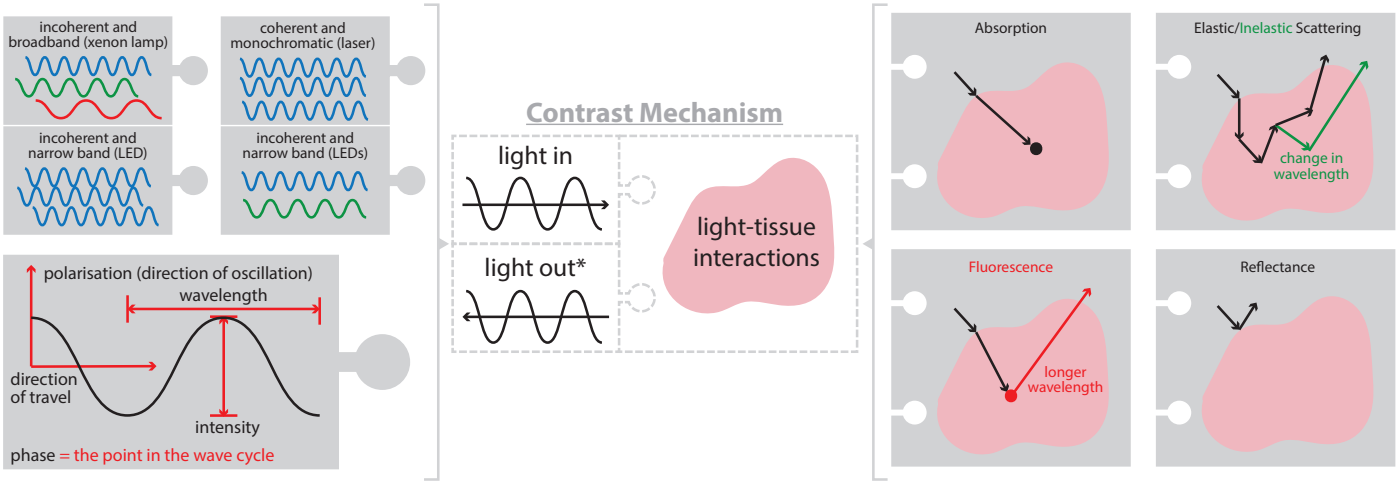
Acronyms

4QB	4-quadrant biopsies
a/LCI	angle-resolved low coherence interferometry
AA	Acetic Acid
ACG	American College of Gastroenterologists[9]
AFI	autofluorescence imaging
AGA	American Gastroenterology Association[107]
ASGE	American Society for Gastrointestinal Endoscopy[18]
BO	Barrett's Oesophagus
BSG	British Society of Gastroenterologists[7]
CARS	coherent anti-Stokes Raman spectroscopy
DRS	diffuse reflectance spectroscopy
eCLE	endoscope-based confocal laser endomicroscopy
ERS	endoscopic Raman spectroscopy
ESGE	European Society of Gastrointestinal Endoscopy[8]
ESS	elastic scattering spectroscopy
ETMI	endoscopic trimodal imaging

FICE	Fujicon Intelligent Colour Enhancement
FLIM	fluorescence lifetime imaging
HD-WLE	high-definition white light endoscopy
LSS	light scattering spectroscopy
MB	methylene blue
MPM	multi-photon microscopy
MSI/HIS	multi-/hyper- spectral imaging
NBI	narrow band imaging
OCT	optical coherence tomography
OFDI	optical frequency domain imaging
OMI	optical molecular imaging
PAE	photoacoustic endoscopy
pCLE	probe-based confocal laser endomicroscopy
SOC	standard of care
TRF	time resolved fluorescence
VLE	volumetric laser endomicroscopy

Figures

Figure 1. Contrast mechanisms. An optical contrast mechanism consists of three elements: illumination, interaction, and detection of light. By carefully controlling the properties of the light illuminating the tissue (left) we can probe specific light-tissue interactions (right). These include reflection, absorption, elastic/inelastic scattering and fluorescence. Advanced endoscopic imaging modalities use these interactions as a source of contrast for detection of dysplasia (centre). Information about the interaction is encoded within the properties of the output light: the wavelength, the distance between peaks in the wave; the polarisation, the direction in which the wave oscillates; the phase, the point in the cycle of the wave; and the intensity, the power within the wave. Detection of these properties allows us to infer information about tissue disease state.



* optoacoustic imaging detects sound out

Table 1. Endoscopic device architectures.

** Theoretically most combinations of contrast mechanism and device type are possible. Here we give the contrast mechanisms that are most compatible with the advantages and disadvantages of the device architecture.

*** Image type is again dependent on contrast mechanism. Here we give the image types for the most compatible contrast mechanisms for the device architecture.

Schematics of each device architecture are shown in Figure 2.

Device Architecture	Example Device (s)	FOV	Advantages/Disadvantages	Most Compatible Contrast Mechanism**	Typical Image Type***	Ref
Forward Facing (Trans-oral)	Standard commercial endoscopes e.g. Olympus, Pentax, Fuji	Wide (typically 140° luminal view)	+ Availability + Familiarity + Wide variety of tools for biopsy, washing, marking + Articulation – Endoscopist must articulate to survey entire surface	WLE, Chromoendoscopy, NBI, eCLE, OMI, MSI/HSI, Polarimetry	En-face, luminal	
Forward Facing (Trans-nasal)	Standard commercial endoscopes e.g. Olympus, Pentax, Fuji	Wide (typically 140° luminal view)	+ Improved patient tolerance and no sedation required + Articulation + Shorter, less costly procedure – Endoscopist must articulate to survey entire surface – **Lower quality image***, narrower working channel inappropriate for interventions, poorer suction and air function and smaller biopsy capabilities compared with trans-nasal endoscopes ***unsuitable for Barrett's surveillance**	WLE, NBI	En-face, luminal	108
Babyscope E.g. Contact Probe	Mauna Kea Cellvizio®	Narrow (10s – 100s microns)	+ Compatible with insertion through working channel of standard endoscopes – Must be used alongside standard endoscope for articulation, washing, biopsy, marking – Contact with lumen must be carefully controlled – Small FOV	pCLE, ERS, ESS/DRS, a/LCI, MSI/HSI, FLIM, MPM, PA, Polarimetry	Spectrum, en-face	109
Balloon Based	NinePoint NvisionVLE®	Volumetric	+ Controlled withdrawal + Potential for cautery marking capability + Compatible with insertion through working channel of standard endoscopes + Allows full volumetric imaging of oesophagus – No biopsy, washing capabilities – Contact with lumen must be carefully controlled	OCT/VLE/OFDI	Volumetric	20,21
Wireless Capsule	Given Imaging PillCam® ESO series	2 x 169° (ESO2)	+ No sedation required + Can be implemented in primary care + Potential for low cost if reusable – One shot (cannot return to suspicious lesions) – No biopsy, washing, marking capabilities – Long delay for capsule to pass (8 – 10 hours) – No control over motion – Contact with lumen must be carefully controlled	WLE, NBI, MSI/HSI, Polarimetry	En-face, luminal or circumferential	29,30,110
Tethered Capsule	No commercial devices	Volumetric	+ No sedation required + Can be implemented in primary care + Potential for low cost if reusable + Controlled withdrawal + Potential for cautery marking capability + Immediate removal of capsule + Allows full volumetric imaging of oesophagus – No biopsy, washing capabilities – Contact with lumen must be carefully controlled	OCT/VLE/OFDI	Volumetric	35
Wide Angle	EndoChoiceFuse (330°)	Extra Wide (>140°)	+ Familiarity + Wide variety of tools for biopsy, washing, marking + Articulation + Wide FOV allows viewing of entire lumen with minimal articulation – Increased cost	WLE, Chromoendoscopy, NBI, eCLE, OMI, MSI/HSI, Polarimetry	En-face, Circumferential	37

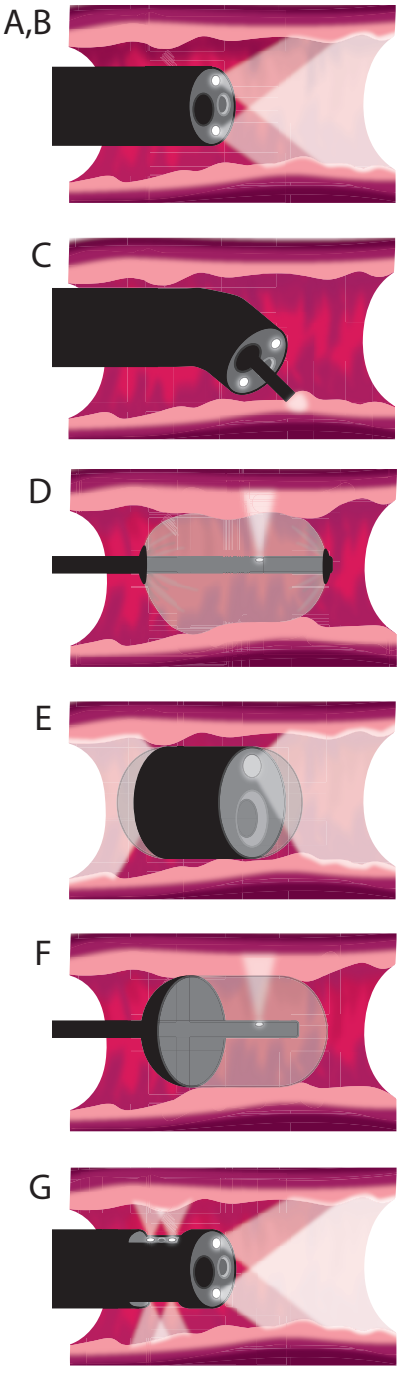


Figure 2. Schematic representations of the endoscopic device architectures listed in Table 1.

A: Forward Facing (Trans-oral)

B: Forward Facing (Trans-nasal)

C: Babyscope E.g. Contact Probe

D: Balloon Based

E: Wireless Capsule

F: Tethered Capsule

G: Wide Angle

Table 2. Advanced optical methods in clinical use for endoscopic BO surveillance.

Example images for each method are shown in **Supplementary Figure 2.**
* cannot be advocated or discouraged at this time

	Advantages	Disadvantages	Sensitivity	Specificity	Recommendation				
					BSG	ASG	ACG	AGA	ESG
HD-WLE + 4QB targeted biopsies and histopahtology	• Widely available • Well established	• Prone to sampling error[11] • Exhaustive biopsies are expensive	0.40-0.68 [15]	0.98-1.00 [15]	✔	✔	✔	✔	✔
Chromoendoscopy	• Inexpensive • Widely available • AA has shown high sensitivity and specificity for detecting dysplasia[18]	• Potential toxicology issues[43] (MB) • Increase in procedure time[18] • Low inter-observer agreement • No current procedural terminology for billing and reimbursement[18] • Difficulty in achieving uniform application of dye[11]	0.92-0.966 (AA) 0.642 (MB) [18,111]	0.846-0.96 (AA) 0.959 (MB) [18,111]	✗	✔ (AA)	✗	✗	✗
Hardware-based Virtual Chromoendoscopy (e.g. NBI, BLI)	• Ability to visualise mucosal and vascular patterns • Widely available • Ease of use • High sensitivity and specificity for detecting HGD[112,113] • Reduced number of biopsies[114]	• No universal classification criteria until recent BING criteria[45] • Low inter-observer agreement • Low sensitivity for LGD[115]	0.942[18]	0.975[18]	✗	✔	✗	*	✗
Software-based Virtual Chromoendoscopy (e.g. FICE, iSCAN)	• No additional hardware costs	• Lack of data	0.83[51] (HGD, FICE)	Unavailable	✗	✗	✗	*	✗
Autofluorescence Imaging (AFI)	• Easy to combine with NBI and WLE	• Many studies biased by comparison with substandard WLE[116] • Limited value in routine surveillence[116]	0.50[117] (HGD)	0.61[117] (HGD)	✗	✗	✗	✗	✗
Endoscopic Trimodal Imaging (ETMI)	• Reduced false positive rate relative to AFI alone	• Useful in tertiary referral centres[56] but not in community practice[57]	0.805[18]	0.46[18]	✗	✗	✗	✗	✗
Probe-based Confocal Laser Endomicroscopy (pCLE)	• Probe can be inserted through working channel of standard endoscope • Close to in-vivo histology	• Often uses exogenous contrast (fluorescein)	0.903[18]	0.773[18]	✗	✗	✗	✗	✗

Endoscope-based Confocal Laser Endomicroscopy (eCLE)	• Close to in-vivo histology	• Requires dedicated endoscope (in contrast to pCLE) • Often uses exogenous contrast (fluorescein)	0.904[18]	0.927[18]	✗ ✔ ✗ ✗ ✗

Table 3. Emerging optical methods for endoscopic BO surveillance.

Example images for each method are shown in **Supplementary Figure 3.**

Blue: ***Exogenous contrast***

Red: ***Interrogating disordered tissue microstructure***

Green: ***Interrogating abnormal tissue function and metabolism***

Purple: ***Interrogating bulk molecular composition***

Orange: ***Multimodal methods***

	Source of Contrast	Biological Change in Cancer	Functional Information	Morphological Information	Depth Sectioning	Strengths/ Weaknesses	Status/ Prospect
Optical Molecular Imaging (OMI)	Exogenous fluorophores conjugated to targeting moieties (lectins, peptides, antibodies, affibodies, enzymes) that targeting intracellular and extracellular proteins and enzymes	Biochemical	✔	✔	✗	+ Specificity – Exogenous contrast – Surface images – Cost	*In vivo* trials in BO[61]. Potential to be translated for wide field surveillance. Awaiting further *in vivo* trials.
Optical Coherence Tomography/ Optical Frequency Domain Imaging/ Volumetric Laser Endomicroscopy (OCT/OFDI/VLE)	Structural features.	Organizational changes, vasculature	✗	✔	✔	+ High resolution + Depth sectioning + Endogenous contrast – Large image datasets	*In vivo* trials in BO (patient series, n=6)[63].
Elastioc Scattering Spectroscopy/ Diffuse Reflectance Spectroscopy/ Light Scattering Spectroscopy (ESS/DRS/LSS)	Endogenous scatterers (cells, nuclei, organelles)	Biochemical, cellular/organelle changes	✔	✗	✗	+ Depth penetration + Endogenous contrast – Spectrum rather than image	*In vivo* trials in BO (single centre pilot study, n=9 patients, n=95 biopsies)[72]. No trials published in last 10 years.
Angle-resolved Low Coherence Interferometry (a/LCI)	Nuclei	Increase in nuclear size	✗	✔	✗	+ High sensitivity and specificity in pilot study + Endogenous contrast – Tissue orientation can affect results	*In vivo* pilot study in BO (2 centre pilot study, n=46 patients, n=172 sites)[73]. Combination with OCT. Clinical trials likely.
Polarimetry	Nanostructural anisotropy	Collagen, cellular orientations, organizational changes	✔	✗	✗	+ Endogenous contrast + Instrumentation challenges	No trials in BO. Awaiting further device development.

Photoacoustic Endoscopy (PAE)	Endogenous absorbers (NAD(P)H, haemoglobin)	Vasculature	✔	✔	✔	+ Volumetric images + Endogenous contrast – Instrumentation challenges – Limited resolution at present – Long acquisition times	*In vivo* imaging of oesophagus in animals[83]. No trials in BO Awaiting application to BO.
Fluorescence Lifetime Imaging (FLIM)	Endogenous fluorophores (NAD(P)H, flavins, collagen, elastin, phenylalanine, tryptophan, tyrosine, melanin).	Biochemical, microenvironment (pH, $[0_2]$, $[Ca^{2+}]$)	✔	✔	✔	+ More robust than traditional AFI + Endogenous contrast – Safety of UV illumination – Long acquisition times	*Ex vivo* trials (TRF) (single centre pilot study, n=37 patients, n=108 fluorescence decay profiles)[86]. Awaiting in vivo trials.
Multi-photon Microscopy (MPM)	Endogenous fluorophores (NAD(P)H, flavins, collagen, elastin, phenylalanine, tryptophan, tyrosine, melanin).	Cell type	✔	✔	✔	+ Depth sectioning + High resolution + Endogenous contrast – Requires high illumination intensity	*Ex vivo* trials in BO (n=25 patients, n=35 biopsies)[92]. Awaiting in vivo trials.
Endoscopic Raman Spectroscopy (ERS)	Specific molecular groups (e.g. C-C proteins, C-C ring of phenylalanine, C-C of lipids, C-N and N-H of proteins, CH_2 of lipids, C=C of porphyrins, C=0 of proteins and lipids)	Biochemical	✔	✗	✗	+ Detailed biochemical information + Algorithms have been developed + Multicentre trials underway – Endogenous contrast. – Spectrum rather than image – Repeatability has been questioned – Validation using ex-vivo tissue is difficult	*In vivo* trials in BO (pilot study, n=450 patients)[95]. Potential to be translated if repeatability can be confirmed. Awaiting multicentre trials.
Coherent anti-Stokes Raman Spectroscopy (CARS)	Specific molecular groups (see ERS)	Biochemical	✔	✔	✔	+ Detailed biochemical information + Increased sensitivity compared to ERS – Instrumentation challenges – Requires high illumination intensity	No trials in BO. Awaiting further device development.
Multi-/Hyper- Spectral Imaging (MSI/HIS)	Endogenous chromophores (NAD)P)H, haemoglobin)	Vasculature, visible lesions	✔	✔	✗	+ Simple + Compact + Endogenous contrast – Surface images	No trials in BO. Awaiting application to BO.

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Contributors

DJW, CRMF and SEB wrote the manuscript, with feedback and clinical guidance from MdP.

Declaration of interests

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Search strategy and selection criteria

We searched PubMed, Scopus and Google for articles published up to Nov 1, 2017 using the terms, “imaging”, “Barrett’s”, “endoscope”, “capsule”, “optical” and “detection”. Additional articles were also identified through searches of the references of these articles. Only papers in English were reviewed. The final reference list was generated on the basis of originality, impact and relevance to the aims of this review.

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